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Newly Diagnosed Glioblastoma: A Review on Clinical Management

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Abstract

Glioblastoma is an aggressive primary tumor of the central nervous system. This review will focus on clinical developments and management of newly diagnosed disease, including a discussion about the incorporation of molecular features into the classification of glioblastoma. Such advances will continue to shape our thinking about the disease and how to best manage it. With regards to treatment, the role of surgical resection, radiotherapy, chemotherapy, and tumor-treating fields will be presented. Pivotal studies defining our current standard of care will be highlighted, as will key ongoing trials that may influence our management of glioblastoma in the near future.

Introduction

Glioblastoma, previously known as glioblastoma multiforme, is the most aggressive among infiltrative gliomas, a group of primary tumors arising from the central nervous system (CNS). Patients with this cancer type face significant morbidity and mortality, with over 13,000 deaths per year in the United States. Recent advances in our biological understanding of gliomas have led to important and substantive changes in their classification, in the

identification of prognostic and predictive molecular markers, as well as in the therapeutic management of newly diagnosed glioma.

Classification

The term ‘glioblastoma multiforme’ was introduced in the 1926 classification system devised by Cushing and Bailey.[1] ‘Multiforme,’ which refers to a heterogenous, histological appearance and proliferation of multiple cell types, was abandoned from the revised nomenclature in the 2007 World Health Organization Classification of Tumors of the Central Nervous System, and is now simply called ‘glioblastoma’. [2] Glioblastoma is histologically defined by neoplastic cells with astrocytic characteristics and the presence of either endothelial proliferation—often in a glomeruloid morphology—and/or necrosis, which may resemble a pseudopalisading pattern (a false fence of neoplastic cells surrounding an area of necrotic tissue).

Due to its aggressive and highly proliferative course, glioblastoma is considered a grade IV astrocytoma. Molecular characterization has allowed for further refinement of the condition’s classification and is now an integral part of the diagnosis of malignant glioma. [3] Patients are classified into one of two distinct categories based on the presence or absence of mutations in the isocitrate dehydrogenase (IDH) 1 (*IDH1*) or *IDH2* genes.

Primary glioblastoma/glioblastoma IDH wild-type (IDH-wt)

The majority of glioblastomas are IDH-wt and correspond to the longstanding clinical description of primary glioblastomas, which arise rapidly from non-neoplastic brain and progress quickly. In addition, a subgroup of lower-grade glioma may carry molecular features and signatures similar to glioblastoma, with a similarly aggressive natural course[4] for which an intensive treatment strategy is advocated. These facts stress that a microscopic histological diagnosis alone is insufficient to make informed and rational clinical decisions; therefore, it is essential that molecular alterations be integrated when diagnosing and managing glioma. This will potentially be of benefit in opening up appropriate clinical trial opportunities for this subset of patients in the future.[5]

Secondary glioblastoma/glioblastoma, *IDH* mutated

Up to 10% of patients with glioblastoma harbor a mutation in the *IDH1* or *IDH2* genes, an early event in gliomagenesis. Since these glioblastomas often arise from a prior, lower-grade glioma, they are considered secondary glioblastoma. In the past, both primary and secondary glioblastoma were considered to be the same clinical entity. However, recent studies clearly indicate that *IDH*-mutated glioblastoma has a more protracted natural course. As such, secondary glioblastomas are to be classified as a distinct biological and molecular entity for which different treatment strategies will ultimately be proposed. Former series of long-term survivors are commonly enriched for patients with *IDH*-mutated tumors.[3]

Epidemiology

Primary CNS tumors represent only 2% of adult cancer diagnoses; however, due to their location and often rapid clinical course, they are associated with high morbidity and

mortality. About 50% of primary malignant CNS tumors are glioblastoma, with an incidence rate of 3.20 per 100,000 population. Incidence is higher in whites than in blacks (3.46 vs 1.79 per 100,000 population, respectively), with a 1.93:1 ratio ($P < .05$), a difference for which no biological explanation exists. Compared with whites, the incidence of glioblastoma is somewhat lower in Asians. The condition occurs more frequently in men than in women, with a 1.58:1 ratio ($P < .05$).[6] Over the last 3 decades, the incidence of glioblastoma in the United States has been relatively stable[7]; however, an aging population and better diagnostic tools may lead to a higher incidence of disease, as has been suggested in other countries[8]. Further study is needed to confirm changes in incidence, and, if present, to determine the causal factors.

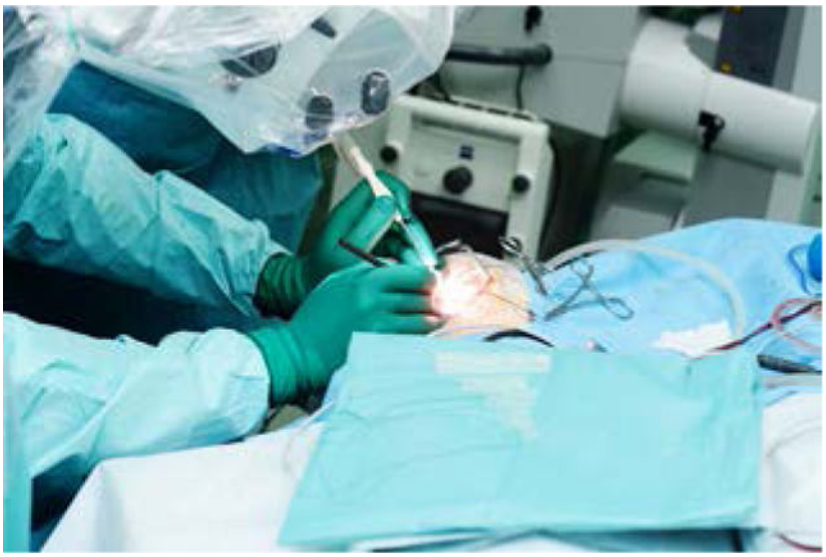
Both environmental and patient-intrinsic factors may influence the risk of developing glioblastoma. An established risk factor is prior exposure to ionizing radiation to the CNS. The lag time between radiation and the development of glioblastoma may range from years to decades.[9–11] Unlike other cancers, there is no histologic or molecular signature that is pathognomonic for radiation-induced glioblastoma. The condition is observed in several hereditary cancer syndromes, including Lynch syndrome (with mutations in *MSH2*, *MLH1*, *MSH6*, *PMS2*) and Li-Fraumeni syndrome (with mutations in *TP53*).[7] While mutations in some tumor suppressor genes increase the risk of susceptibility, the presence of an allergic disorder appears to be associated with a decreased incidence of glioma, including glioblastoma, across a number of epidemiologic and preclinical studies.[7,12–14]

Pathophysiology

Despite extensive study, the cellular origin of glioblastoma and the pathophysiologic mechanism of gliomagenesis remain uncertain. Research on the cell of origin for glioblastoma often involves targeting different precursor cell populations in transgenic mouse models and explores the effects of these interventions on the development of glioma. However, contemporary thought favors primitive pluripotent cells, including neural stem cells, glial precursor cells, and oligodendrocyte precursor cells.[15] Numerous preclinical models have been conducted in this area, each with their favorable attributes and drawbacks.[16–19]

Research demonstrates that, amongst IDH-wt glioblastomas, there are spatial intratumoral differences in the mutational profile and clonality of tumor cells, with approximately half of the mutations being regionally exclusive. Distinct areas, found within these tumors, can exhibit a hypermutated phenotype. When present, mutations in the *TERT* gene appeared across all clones.[20] Recent studies utilizing xenografts in murine models have shown that these tumors consist of a slow-cycling population of stem-like cells which give rise to a rapidly dividing progenitor cell population, a proportion of whose daughter cells develop into terminal differentiated cells, supporting a hierarchical model of gliomagenesis. [21] A minority of the clonal population proves resistant to chemotherapy.[21] In turn, this cell population will require different treatments. When evaluated longitudinally, recurrent glioblastoma can accumulate additional mutations[22], and can appear similar to the primary tumor *or* may resemble a distinct subclonal population.[23,24] It is thought that this genomic heterogeneity is driven, at least in part, by the uneven cellular inheritance patterns of extra-

chromosomal DNA. [25] As we garner a clearer understanding of the pathophysiology of gliomagenesis, new areas for potential therapeutic intervention will open up.



In glioblastoma, surgery plays an important diagnostic and therapeutic role: it offers tissue for diagnosis, immediate relief of the tumor-related mass effect and its associated symptoms, and potential cytoreduction.

In addition to the difficulties associated with treating heterogenous tumors, which evolve over the course of the disease and harbor treatment-resistant subpopulations of cells, the blood-brain barrier is another impediment to the effective treatment of these tumors. The blood-brain barrier is a dynamic, functional system which both precludes and modulates the traversing of systemically administered therapeutics into the CNS, including CNS tumors. [26] Numerous means have been utilized to overcome this obstacle. Thus far, the most successful have included systemically-administered drugs with adequate CNS penetration (eg, temozolomide) and locally delivered, alternating electrical fields (tumor-treating fields, TTFields). Direct intracranial application of both chemotherapy (eg, biodegradable carmustine–impregnated wafers) and radiation (eg, brachytherapy) has also been explored.

Intratumoral injection of oncolytic viruses and chimeric antigen receptor (CAR) T-cell therapies is a modern example of a similar strategy that is undergoing active investigation. [27,28] Disruption of the blood-brain barrier to facilitate transmission of a systemically-administered therapy has been under investigation for many decades. Initial studies utilized intra-arterially–administered agents.[29] A recent strategy being studied includes ultrasound to open up the barrier.[30] Another, which has had varying degrees of success, is avoiding the need to overcome the blood-brain barrier. The utilization of therapeutics whose direct activity occurs on the luminal side of the blood-brain barrier (eg, bevacizumab)[31]—or which act on the luminal side, with a goal of affecting function on the tumoral side of the barrier (eg, immune checkpoint inhibitors)—is another way to attempt to circumvent this obstacle. It is reasonable to surmise that more than one approach may prove to be successful.

Therapeutic Management

The therapeutic management of newly-diagnosed glioblastoma typically involves a four-pronged approach. First, surgical resection is completed to the maximal safe extent, thereby reducing the tumor load and establishing a histopathological and molecular diagnosis. Following surgery, adjuvant radiotherapy is given with concomitant and maintenance chemotherapy, as is treatment of alternating electrical fields.

Surgery

Surgery plays an important diagnostic and therapeutic role in the management of glioblastoma: it offers tissue for histological and molecular diagnosis, immediate relief of the tumor-related mass effect and its associated symptoms, and potential cytoreduction. However, due to the invariably infiltrative nature of the disease, even macroscopically complete resection is not curative. Numerous retrospective studies have evaluated the value of the extent of resection in glioblastoma. While early work suggested a dichotomous picture with a need for a substantial extent of resection of the contrast-enhancing tumor,[32] subsequent studies demonstrated the graded benefit of the extent of resection. [33,34] A more recent meta-analysis also supports a more extensive resection with improved 1- and 2-year survival rates as well as prolonged progression-free survival.[35] In low-grade glioma, the extent of resection is influenced by the area of increased signal on T2/fluid-attenuated inversion recovery (FLAIR) imaging.[36–39] Similarly, glioblastoma tumors are not limited to the area of enhancement but rather involve the area of increased T2/FLAIR signal. The extent of resection of this non-enhancing glioblastoma may also be of clinical impact, as demonstrated in a recent retrospective study.[40]

Although the association between extent of resection and survival has been reported and consistently confirmed in numerous studies, it is subject to several potential confounders, biases, and occult prognostic factors. While cytoreduction—the act of removing the bulk of tumor cells—may intuitively delay disease recurrence, the non-linear growth of tumor cells seen in glioblastoma could quickly recover the tumor burden that was removed during surgery, negating the survival benefit of small increments of cytoreduction. The durability of the effect of cytoreduction, and whether it leads to a survival benefit, is likely related to the rate of tumor cell proliferation. On the other hand, patients with neurological deficits have lower functional status, which ultimately impacts their overall survival. Thus, it is possible that relief of mass effect leading to improved functional status from resection might prolong survival in symptomatic patients, irrespective of cytoreduction. Finally, the tumor location may also reflect the underlying biology and dictate the natural history of the disease. Determination of the influence of these previously described variables on overall survival is complicated, as resectable tumors may have an overall better prognosis, regard-less of the actual extent of resection.

Resectable tumors often present in “silent areas of the brain” that tolerate injury for a long period of time prior to becoming symptomatic. In addition, resectable tumors, such as fronto-polar tumors, are more likely to harbor *IDH1* mutations, which are associated with a better prognosis. In contrast, unresectable tumors, such as midline/diencephalic or brainstem tumors, often bear H3K27 mutations, which indicate an overall more aggressive biology and

a worse prognosis.[41] Further dissection of the relationship between the extent of resection and survival requires controlling for tumor resectability per se. Yet, this complicated variable is difficult to capture by established scales, and is influenced by anatomical considerations as well as neurosurgeon-related factors.[42]

Maximizing extent of resection.—A number of technological advances have been developed to safely maximize the extent of resection, although their availability and usage may vary greatly. These techniques have become more widespread over time because, in addition to maximizing the extent of resection, they also optimize the safety of intra-axial brain tumor surgery. The major technological tools that surgeons use for improving the safety and accuracy of resection can be divided into three groups, as follows.

Intraoperative navigation technology.: This technology involves the use of volumetric imaging (eg, MRI or CT scan), which is used as a reference to locate a lesion/anatomical structure within the surgical field. Navigation involves an optical or electromagnetic system that uses a physical reference to register the location and position of a patient's head in space, and allows real-time visualization of instruments within the images, which are loaded to a computer. These technologies help minimize the extent of the open craniotomy exposure; optimize a trajectory to access lesions that avoids critical neural structures, such as white matter pathways; and provides an anatomical reference during the operation. However, they are limited by the fact that the referenced images are not updated as resection progresses, and brain shift in space in relation to the skull makes this information less reliable as the case advances. To address this, several groups have introduced intraoperative MRI, which provides a real-time update of the field for navigation.[43,44] The true utility and cost-effectiveness ratio of intraoperative MRI remains a highly debated topic, as cost and added time during the procedure are not insignificant. The use of intraoperative ultrasound is a dynamic, easy to use, and affordable alternative for real-time imaging during surgery.

Electrophysiological monitoring and functional brain mapping.: Wilder Penfield and George Ojemann pioneered the use of electrodes to functionally map sensory and motor primary cortical regions and related subcortical circuits as the spinothalamic and corticospinal tracts to avoid postoperative deficits. [45–48] Over the last few decades, work by George Ojemann, Hugues Duffau, Mitchell Berger, and others has incorporated the routine use of awake brain mapping techniques, which have greatly improved the surveillance of motor circuits, language/comprehension, coordination, vision, and some higher cognitive functions by enabling them to be mapped and preserved.[49–53]

Fluorescent markers to maximize tumor visualization.: Fluorescent dyes—which are either metabolized by tumor cells, or accumulate in areas of blood-brain barrier breakdown —have been incorporated to maximize tumor tissue visualization in the operating room. This is helpful, as gross tumor tissue often has a similar texture or color as the surrounding edematous brain and is not always easy to distinguish under bright light. The use of 5-aminolevulinic acid under blue light allows the neurosurgeon to view residual tumor in real-time during surgery. A phase III trial demonstrated an improved rate of complete resection

for contrast-enhancing tumor with 5-aminolevulinic acid compared with conventional microsurgery with white light (65% vs 36%; $P < .0001$) and 6-month progression-free survival (41% vs 21%; $P = .0003$). However, this did not translate into an improvement in overall survival.[54] Fluorescein has also been used to visualize enhancing tumor, as this dye leaks through areas with defective blood-brain barrier.[55,56] Here, no special light source is needed.

Radiation therapy

Radiotherapy has been shown to improve survival in glioblastoma and plays a key role in treatment. Modern conformal radiotherapy—which utilizes three-dimensional, computerized planning and multi-beam modulation—focally treats MRI-evident disease plus margin to a cumulative absorbed dose of 60 Gy. Given in daily doses of 1.8 to 2.0 Gy fractions, total treatment lasts approximately 6 weeks and is usually initiated 3 to 4 weeks after surgery. While some reports have suggested that delayed radiotherapy has a detrimental effect, other investigators have reported better outcomes; this question has yet to be definitively answered.[57,58]. Up to 6 to 7 weeks of postoperative recovery is considered acceptable as part of the established standard of care.

Earlier studies have examined doses of more than 60 Gy, some of which incorporated stereotactic radiosurgery. However, they failed to demonstrate improved outcomes with doses of up to 76 Gy.[59] An ongoing randomized phase II study, NRG BN001 (ClinicalTrials.gov identifier: NCT02179086), is evaluating dose escalation to 75 Gy compared with standard 60 Gy radiotherapy.[60] This study includes distinct cohorts utilizing photons *or* protons, and the primary endpoint is survival.

For elderly patients or those with sub-stantially altered performance status and poor prognosis, an abbreviated course of “hypofractionated” radiotherapy allows for a shortened overall treatment time. Long-term toxicity is of less concern in this population due to a commonly short survival. Hypofractionated radiation, which has been widely investigated, has been utilized to improve tolerability of radiotherapy (Table 1). Tumor volume often guides the selection of a radiation regimen because the risk of toxicity is theoretically greater with high vs low daily doses. Omitting radiotherapy (even less than the standard 60 Gy) leads to significantly worse survival compared with best supportive care alone.[61] Recent prospective data have demonstrated that abbreviated courses can also be safely and effectively combined with concurrent chemotherapy, as covered in the section below regarding treatment strategies for elderly patients.

A direct prospective comparison between full-course radiotherapy with concurrent and adjuvant chemotherapy vs abbreviated course radiotherapy with concurrent and adjuvant chemotherapy has not been conducted. In addition to an abbreviated course of radiotherapy, the shorter course also employs a shorter course of concomitant chemotherapy. This lack of direct comparison leaves an important question not fully answered. In many clinical practices, the full course of radiotherapy and chemotherapy will be utilized in elderly patients with good performance status.

Systemic therapy

We recently reviewed in detail the pivotal, late-phase trials that led to the current standard of care for patients with newly diagnosed glioblastoma.[62] These trials are summarized in Table 2. Temozolomide is a DNA-alkylating chemotherapy agent that is designed to readily cross the blood-brain barrier to achieve therapeutic concentrations in the brain. In 2005, a large, international, randomized, phase III trial (European Organisation for Research and Treatment of Cancer [EORTC] 26098/National Cancer Institute of Canada [NCIC] CE3) demonstrated prolonged survival when daily temozolomide chemotherapy (75 mg/m2 daily × 40–49 days) is added concomitantly to radiotherapy followed by 6 cycles of maintenance temozolomide (150–200 mg/m2 × 5/28 days). Based on this landmark trial, temozolomide/radiotherapy followed by maintenance temozolomide has become the world-wide standard of care for patients with a newly diagnosed glioblastoma.[63,64] Temozolomide adds a methyl group to the DNA residues at the O6, N3, and N7 positions that, if unrepaired, leads to DNA strand breaks and cytotoxicity. More than one-third of glioblastomas are deficient in methylguanine methyltransferase (MGMT), a repair protein that removes the methyl adduct from the O6 guanine position. This MGMT deficiency is via methylation (silencing) of the *MGMT* gene promoter, which leads to downregulated transcription. Glioblastoma patients with a silenced *MGMT* gene who are treated with an alkylating agent chemotherapy have a longer survival than those with an unmethylated *MGMT* and those treated with radiotherapy alone.[65] In studies of paired tissue samples, *MGMT* promoter methylation is relatively conserved from the newly diagnosed to progressive disease settings, with the majority of tumors maintaining an unchanged profile over time.[66,67] In mismatch repair–deficient conditions, the O6 guanine methyl adduct is tolerated and can be mutagenic. This may be a key mechanism in the development of glioma mutations due to temozolomide, and is described in low-grade glioma progressing to higher grade tumors as well as potentially in the development of a hypermutated phenotype.[68,69] The methyl adducts at N3 and N7 are addressed by the base excision repair mechanism.[70] Inhibition of this mechanism continues to undergo investigation in trials of poly (ADP-ribose) polymerase-1 (PARP) inhibitors.

Optimal duration of adjuvant temozolomide chemotherapy.—The pivotal EORTC/NCIC study established a regimen of up to 6 adjuvant chemotherapy cycles. However, in the United States, the duration of chemotherapy may still extend for up to 12 cycles or more in non-progressive patients. While early treatment discontinuation is a concern due to the disease's poor prognosis, cumulative toxicity, impaired bone marrow reserve for subsequent second-line chemotherapy, and increased risk of secondary malignancies are concerns with prolonged treatment. In some trials, treatment was allowed per local practice to be extended to up to 12 cycles. A pooled meta-analysis of individual patient outcomes data stemming from four randomized trials compared the duration of maintenance temozolomide chemotherapy (6 cycles vs 7+ cycles) among individuals who were non-progressive after 6 cycles.[71] While there was a slight improvement in progression-free survival, no difference in survival was seen for those who received 6 cycles vs more than 6 cycles of chemotherapy. This suggests that prolonged administration and dose intensification do not improve disease control. At this time, the value of temozolomide during radiotherapy, independent of adjuvant temozolomide in the treatment of glioblastoma, is unknown.

Alternative temozolomide dosing schedules.—Alternative dosing schedules have been investigated in the newly-diagnosed and recurrent disease settings. However, none of these regimens have been shown to be superior to the standard temozolomide dosing schedule. The randomized RTOG0525 study found no benefit with intensified maintenance chemotherapy. Patients were randomized at the end of chemoradiotherapy to either standard maintenance therapy (150–200 mg/m2/day × 5/28 days) or an intensified daily regimen (75 mg/m2/day × 21/28 days), effectively doubling the cumulative dose of chemotherapy. No difference in outcomes was noted, and a higher incidence of grade 3/4 toxicities was observed in the investigational arm.[72]

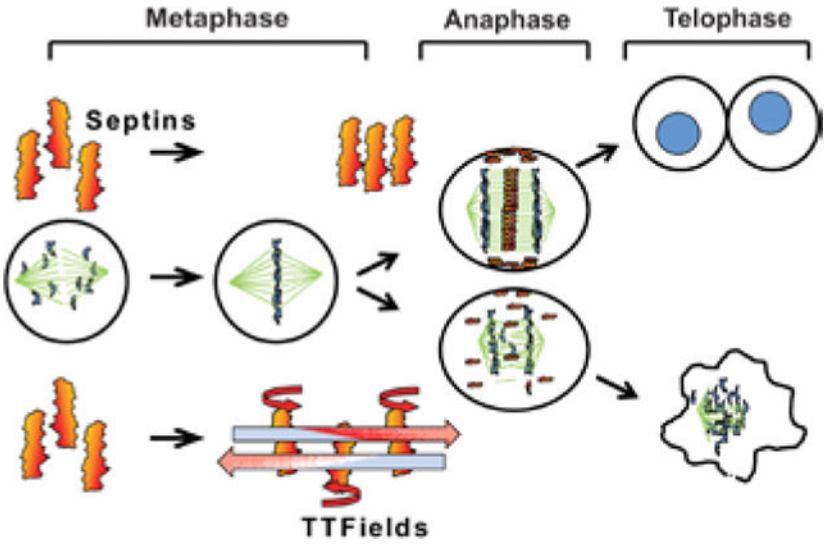
Hopes and disappointments with bevacizumab.—The addition of the antiangiogenic agent bevacizumab to radiotherapy and temozolomide has been explored in two phase III trials focusing on newly diagnosed glioblastoma[73,74] and one phase III trial focusing on recurrent glioblastoma[75]. The observed and expected improvement in progression-free survival based on imaging did not translate into any improvement in overall survival when bevacizumab was added. Unplanned post-hoc analyses found an association of improved overall survival in a molecularly-defined subset of patients.[76] The addition of bevacizumab to hypofractionated radiotherapy demonstrated no improvement in overall survival compared with hypofractionated radiotherapy alone in elderly (≥ 65 years) patients with newly diagnosed glioblastoma.[77] Based on the results of these trials, bevacizumab should not be administered as part of primary treatment of glioblastoma. Of note, some physicians utilize bevacizumab as a corticosteroid-sparing agent to decrease cerebral edema, so that treatment with standard radiotherapy and chemotherapy is feasible without high doses or prolonged use of corticosteroids.

De-escalation of treatment in the elderly.—De-escalation of therapeutic interventions has been extensively explored in the elderly and in frail populations with glioblastoma. This interest is driven by the overall brief survival of elderly glioblastoma patients, and thus the desire to shorten the duration of medical intervention. This topic has recently been reviewed in detail.[78,79] Several studies have prospectively evaluated abbreviated courses of radiotherapy in these patients (as covered earlier in the “Radiation Therapy” section).

Two large randomized trials have evaluated the exclusive administration of temozolomide chemotherapy in the elderly. Consistently, both trials demonstrated that withholding radiotherapy and instead treating patients with temozolomide alone may be an option for elderly patients with tumors harboring a methylated *MGMT* gene promoter, while this strategy is detrimental in the absence of *MGMT* methylation.[80,81] Monotherapy with temozolomide offers the advantage of an oral treatment regimen without the need for daily radiotherapy. The utilization of a short-course, hypofractionated radiotherapy regimen (of 40 Gy in 15 treatments) with concomitant temozolomide, followed by adjuvant temozolomide, was shown to improve outcomes in the elderly, which is consistent with the observed benefit reported 10 years earlier by the EORTC/NCIC in patients up to age 70 years. [82] The clinical circumstances, including chronologic age, performance status, concurrent medical problems, *MGMT* promoter methylation status, and logistical concerns should all be weighed during therapeutic decision-making for elderly patients with glioblastoma. In

healthy, *MGMT*-methylated elderly patients with good performance status, a more aggressive approach, including full-course radiotherapy and temozolomide, can be considered.

Poor performance status.—Both de-escalation and escalation of care for patients with poor performance status have been considered. Many of these evaluations have been performed specifically in the elderly population, thus potentially limiting their generalizability to younger patients. De-escalation approaches attempt to limit the toxicity of treatment in a patient population that may not tolerate and is less likely to benefit from therapy. These approaches also attempt to shorten treatment duration as well as the amount of travel to the treatment facility, particularly for patients with limited mobility. The previously discussed abbreviated radiotherapy courses for elderly patients are also often used in the frail population with a poorer performance status; some prospective studies on abbreviated radiotherapy included patients on the basis of performance status alone.[83,84] The use of temozolomide chemotherapy alone has been studied in patients with poor performance status (Karnofsky Performance Score [KPS] of < 70); it was shown to be associated with an improvement in performance status or an improvement to the level of self-care (KPS ≥ 70) in one-third and one-fourth of patients, respectively. [85] Increasing the number of concomitant therapeutics has been performed with the goals of extending survival and improving functionality. One treatment intensification approach adds bevacizumab to the standard of care, relying on the corticosteroid-sparing effects described earlier. This approach has demonstrated only a transient improvement in performance status, and the data thus far do not justify its routine employment, as median overall survival remained short at 5.6 months (95% CI, 4.4–6.4).[86]



The addition of tumor-treating fields to maintenance temozolomide chemotherapy for newly-diagnosed glioblastoma patients has recently been incorporated as a new standard of care.

TTFields

The addition of TTFields to maintenance temozolomide chemotherapy for newly-diagnosed glioblastoma patients has recently been incorporated as a new standard of care.[87–89] TTFields are applied via multiple electrodes that are directly fixed to the scalp. These low-intensity, alternating electrical fields of 200 Hz interfere with polar organelles (eg, tubulins), which are required for normal cell division. Mitotic disruption ultimately leads to cell cycle arrest, aneuploidy, and apoptosis.[90,91] Additional mechanisms potentially contributing to therapy-associated effects include a disruption of organelles and an induction or modulation of the anti-glioma immune response.[92]

The effect of TTFields was evaluated in two large prospective, non-blinded randomized trials. In recurrent disease, TTFields failed to show superiority over best physicians' choice (chemo)therapy in patients with recurrent glioblastoma. [93] In a pivotal large, randomized, phase III trial, *695* patients with newly diagnosed glioblastoma were randomized to receive adjuvant temozolomide and TTFields or standard maintenance therapy of temozolomide alone after the end of initial treatment with temozolomide/radiotherapy. Patients who received adjuvant temozolomide and TTFields fared much better than those treated with temozolomide alone. Survival was prolonged with a hazard ratio of 0.63 (95% CI, 0.52–0.76; $P < .001$), and durable survival was achieved in some patients. [88] This improvement was observed without a measurable negative impact on health-related quality of life (HRQL). [94] In the real-world setting, the rate of compliance among patients utilizing TTFields is high.[95] The primary toxicity noted in the trials was mild-to-moderate cutaneous toxicity, which typically resolves with minimal intervention.[96]

Impact of Other Medications

It has been hypothesized that certain medications commonly used to treat other conditions may potentially benefit patients with glioblastoma. These range from those prescribed for tumor-related conditions—such as epilepsy[97,98] and cerebral edema—to those which are independent of the neoplastic disease, including hypertension, hyperlipidemia, and venous thromboembolism[99,100]. Thus far, none have been proven to be beneficial. When thoroughly evaluated, none of the associations observed in several studies could be validated in larger cohorts, underscoring the importance of prospective (rather than retrospective) trials with strong biological hypotheses.

Corticosteroids

Corticosteroids are frequently used to decrease cerebral edema. Their off-target effects also lead to the suppression of immune system activity. Recent preclinical and clinical work suggests that these unfavorable effects contribute to shortened survival.[101] This is of particular importance as we evaluate the role of immunotherapeutic approaches for the treatment of glioma.[102] Despite the lack of a clear benefit in survival, bevacizumab has been shown to decrease the utilization of corticosteroids in patients with glioblastoma in numerous trials.[73,74,103–105] In routine clinical practice, functional improvement is often seen in association with radiographic improvement; however, it has not been proven to correlate with improved overall survival.

Future Directions

Efforts are continuously being undertaken to improve outcomes for patients with newly diagnosed glioblastoma. The diminishing return of second-and subsequent-line oncologic therapies supports the testing of promising new therapeutic approaches in the newly diagnosed population. This is underscored by the strong survival benefit seen among patients treated with TTFields in the newly diagnosed setting compared with those with progressive disease. A number of novel regimens are being studied in the newly diagnosed setting (Table 3). While many contemporary trials for newly diagnosed glioblastoma build upon the standard of care, as previously described, trials for patients with unmethylated MGMT promoter may omit temozolomide without losing treatment efficacy.[106–108]

EGFR remains an attractive therapeutic target, as it is frequently upregulated in glioblastoma, and its expression is associated with a worse prognosis; it is constitutionally activated in 30% of glioblastomas with a VIII variant. However, randomized trials targeting EGFR have repeatedly failed.[109,110] The addition of a novel peptide vaccine, rindopepimut, to the standard of care has been studied in a phase III trial. While the preclinical and early-phase studies held substantial promise, the phase III trial failed to demonstrate improved survival.[110] Phase III trial evaluation of the antibody drug conjugate depatuxizumab mafodotin (ABT-414) in combination with standard of care treatment for patients with EGFR-amplified, newly diagnosed glioblastoma is eagerly awaited.[111] Finally, the results of two separate trials evaluating the anti-PD1 monoclonal antibody nivolumab in newly diagnosed glioblastoma patients with unmethylated (CheckMate-498)[112] and methylated (CheckMate-548)[113] MGMT promoter are anticipated. Biomarkers that may help predict benefit from immuno-therapies[114] will require prospective evaluation, but may provide insight into the role of immunotherapeutic approaches in glioblastoma.

Conclusion

The therapeutic management of newly diagnosed glioblastoma is well-defined and includes surgery, radiation, temozolomide, and TTFields. Nuances to management in the elderly or frail exist; in these populations, treatment de-escalation is often considered on a patient-specific basis. The addition of other systemic therapies—such as antiangiogenic agents or other routinely administered medications, such as anti-epileptic or blood pressure agents—has not been shown to improve survival in newly diagnosed glioblastoma. Concerns exist, substantiated by both preclinical and clinical data, that corticosteroid utilization may negatively impact outcomes of immunotherapeutic approaches for the treatment of these patients. This will need to be carefully considered in the design, administration, and interpretation of clinical trials for this disease. As outcomes in glioblastoma remain poor, continued investigation into promising therapeutics is necessary.

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Table 1

Clinical Trials Investigating Various Radiation Dosing Regimens

Author	Minimum Age	Fractional Dose	Total Dose	Duration	Concurrent Chemotherapy?	Median Survival
Baumann et al (1994)[83]	65 y (or KPS ≤ 50)	3.0 Gy	30.0 Gy	10 d	No	6 mos
Roa et al (2004)[115]	60 y	2.67 Gy	40.0 Gy	15 d	No	5.6 mos
Malmstrom et al (2012)[81]	60 y	3.4 Gy	34.0 Gy	10 d	No	7.5 mos
Roa et al (2015)[84]	65 y (or KPS 50–70)	5.0 Gy	25.0 Gy	5 d	No	7.9 mos
Perry et al (2017)[82]	65 y	2.67 Gy	40.0 Gy	15 d	Yes	9.3 mos

KPS = Karnofsky Performance Status.

Table 2

Key Late-Phase Clinical Trials for Newly Diagnosed Glioblastoma

Trial Designation	Author	Year	Phase	n	Age	Study Design	Median OS	Median PFS
N/A	Walker[116]	1978	III	222	NR	*HGG patients* BCNU/RT+ BCNU vs BCNU vs RT vs Supportive care	34.5 wks vs 18.5 wks vs 35 wks vs 14 wks	NR
N/A	Westphal[117]	2003	III	240	18–65 y	*HGG patients* BCNU-wafers + RT vs Placebo-wafers + RT	13.9 mo vs 11.6 mo in HGG patients 13.5 mo vs 11.4 mo in GBM subgroup	5.9 mo vs 5.9 mo in HGG patients
EORTC 26981/22981; NCIC CE3	Stupp[63–64]	2005	III	573	18–71 y	RT/TMZ + TMZ vs RT	14.6 mo vs 12.1 mo	6.9 mo vs 5.1 mo
N/A	Keime-Guibert[61]	2007	N/A	85	≥ 70y	RT/supportive care vs Supportive care	29.1 wks vs 16.9 wks	14.9 wks vs 5.4 wks
RTOG 0525	Gilbert[72]	2013	III	833	≥ 18 y	RT/TMZ + TMZ [150–200 mg/m2/d for 5/28 d) vs RT/TMZ + TMZ (75 mg/m2/d for 21/28 d]	16.6 mo vs 14.9 mo	5.5 mo vs 6.7 mo
RTOG 0825	Gilbert[73]	2014	III	637	≥ 18 y	RT/TMZ/bev + TMZ/bev vs RT/TMZ + TMZ	15.7 mo vs 16.1 mo	10.7 mo vs 7.3 mo
AVAglio	Chinot[74]	2014	III	921	≥ 18 y	RT/TMZ/bev + TMZ/bev vs RT/TMZ + TMZ	16.8 mo vs 16.7 mo	10.6 mo vs 6.2 mo
CENTRIC EORTC 26071–22072	Stupp[118]	2014	III	545	≥ 18 y	*MGMT methylated* RT/TMZ/cilengitide + TMZ/cilengitide vs RT/TMZ + TMZ	26.3 mo vs 26.3 mo	10.6 mo vs 7.9 mo
GLARIUS	Herrlinger[107]	2016	II	182	NR	RT/bev + bev/CPT11 vs RT/TMZ + TMZ	16.6 mo vs 17.5 mo	9.7 mo vs 5.99 mo
ACT IV	Weller[110]	2017	III	745	≥ 18 y	*Enrolled after completion of RT/TMZ*		
						TMZ/rindopepimut vs TMZ	21.1 mo vs 20.0 mo	8.0 mo vs 7.4 mo
EF-14	Stupp[87,88,93]	2017	III	695	≥ 18 y	*Enrolled after completion of RT/TMZ*		
						TMZ/TTFields vs TMZ	20.9 mo vs 16.0 mo	6.7 mo vs 4.0 mo
CCTG CE.6, EORTC 26062–22061, TROG 08.02	Perry[82]	2017	III	562	≥ 65 y	Short-course RT/TMZ + TMZ vs Short-course RT	9.3 mo vs 7.6 mo	5.3 mo vs 3.9 mo
CeTeG/NOA-09	Herrlinger[119]	2019	III	141	18–70 y	*MGMT methylated*		
						RT/TMZ + TMZ vs RT/CCNU/TMZ + CCNU/TMZ	31.4 mo vs 48.1 mo	16.7 mo vs 16.7 mo

bev = bevacizumab; BCNU-wafers = carmustine wafers; CCNU = lomustine; CCTG = Canadian Cancer Trials Group; CPT11 = irinotecan; EORTC = European Organisation for Research and Treatment of Cancer; GBM = glioblastoma; HGG = high-grade glioma, including glioblastoma; N/A = not available; NCIC = National Cancer Information Center; NR = not reported; OS = overall survival; PFS = progression-free survival; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; TMZ = temozolomide; TROG = Trans Tasman Radiation Oncology Group; TTFields = tumor-treating fields.

Table 3

Ongoing Late-Phase Clinical Trials for Newly Diagnosed Glioblastoma

Trial Designation	NCT Number	Phase	Planned n	Novel Treatment	Treatment Regimen	Status
RTOG 3508A (Intellancel)	NCT02573324[111]	IIb/III	640	ABT-414, an EGFR-targeting antibody-drug conjugate	*EGFR amplified or EGFRvIII mutated* RT/TMZ + TMZ vs RT/TMZ/ABT-414 + TMZ/ABT-414	Completed accrual
A071102	NCT02152982[120]	II/III	440	Veliparib, a PARP inhibitor	*MGMT promoter methylated* Post-RT/TMZ enrollment TMZ +/− TTF[a] vs TMZ/veliparib +/− TTF[a]	Completed accrual
N/A	NCT00045968[121,122]	III	348	DCVax®-L, an autologous dendritic cell vaccine	Post-RT/TMZ enrollment TMZ/placebo vs TMZ/DCVax®-L	Completed accrual[b]
CheckMate-548	NCT02667587[112]	III	693	Nivolumab, a PD-1 antibody	*MGMT promoter methylated* RT/TMZ + TMZ vs RT/TMZ/nivolumab + TMZ/nivolumab	Completed accrual
CheckMate-498	NCT02617589[111]	III	550	Nivolumab, a PD-l antibody	*MGMT promoter unmethylated* RT/TMZ + TMZ vs RT/nivolumab + nivolumab	Completed accrual
N/A	NCT03345095[123]	III	750	Marizomib, a proteasome inhibitor	RT/TMZ + TMZ vs RT/TMZ/marizomib + TMZ/marizomib	Open to accrual

[a]Decision to use TTFields is made prior to enrollment but is then continued throughout study treatment.

[b]Preliminary results

DCVax®-L = lysate-pulsed dendritic cell vaccine; NCT = National Clinical Trial; PD-1 = programmed death ligand 1; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; TMZ = temozolomide; TTFields = tumor-treating fields.